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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/530,249	04/04/2005	Masahiko Terakado	Q87291	9920
65565 7590 04/05/2007 SUGHRUE-265550 2100 PENNSYLVANIA AVE. NW WASHINGTON, DC 20037-3213			EXAMINER MURRAY, JEFFREY H	
			ART UNIT	PAPER NUMBER
			1609	
SHORTENED STATUTORY PERIOD OF RESPONSE		MAIL DATE	DELIVERY MODE	
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Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary

Application No.

10/530,249

Applicant(s)

TERAKADO ET AL.

Examiner

Jeffrey H. Murray

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 15 February 2007.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-80 is/are pending in the application.
- 4a) Of the above claim(s) 3-67, 69-76 and 80 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1, 2 and 68 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: _____

DETAILED ACTION

Claims 1-80 are pending in this application.

Election/Restrictions

1. Applicant's election of Group XV in Paper No. 16 is acknowledged. Applicant distinctly and specifically pointed out that the election has been made without traverse. The restriction requirement is deemed proper and therefore made FINAL. Claims 77-79 have been cancelled. Claims 3-67, 69-76, and 80 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention. Applicants are expected to limit the claims in the scope of the elected subject matter.

Specification

2. The disclosure is objected to because of the following informalities:
Page 5 of the specification, line 22 is vague. The phrase "A represents an acidic group" is written, but no "A" is seen in formula I or earlier in the specification. Appropriate correction is required.

The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any of the errors of which applicant may become aware of in the specification.

Abstract

3. The abstract of the disclosure is objected to because it exceeds 150 words in length. The maximum length for an abstract is 150 words. See MPEP § 608.01(b). Appropriate correction is required.

Claim Objections

2. Claim 1 objected to because of the following informalities: Claim 1 recites, "A represents an acidic group." There is no A in formula I. It is believed the applicant meant to refer to Z in formula I, not A. Appropriate correction is required.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1-2, and 68 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for (4-{2-[(3,5-dimethoxy-4-methylphenyl)-(hydroxy)methyl]-5-phenylpentyl}phenyl)acetic acid, does not reasonably provide enablement for numerous other A, B, D, and E rings and R¹, R², R³, R⁴, or R⁵ groups. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

The nature of the invention in the instant application has claims which embrace a diversity of chemically and physically distinct compounds. The applicant has elected to restrict their invention to formula I-B. Claim 68 is a dependent claim of Claim 1. It states that within formula I-B, an A, B, D, and E ring exist. Rings A, B, and D may be monocyclic or bicyclic carbocyclic rings or they could also be monocyclic or bicyclic heterocyclic rings, whereas the E ring may not be bicyclic. For each ring, there is a substituent, $(R^1)_p$, $(R^2)_q$, $(R^3)_r$, $(R^4)_s$, and (R^5) . The p, q, r and s represent that this R group may appear from one to five times on the A, B, D and E rings. The R groups are defined within Claim 68 as a Markush group with a large variety of possible groups ranging from a small simple alkyl group to a larger group such as a sulfonamide or a carboxylic ester.

Within the specification, applicants have shown only one representative example of a compound of formula I-B being synthesized, (4-{2-[(3,5-dimethoxy-4-methylphenyl)-(hydroxy)methyl]-5-phenylpentyl}phenyl)acetic acid. (4-{2-[(3,5-dimethoxy-4-methylphenyl)-(hydroxy)methyl]-5-phenylpentyl}phenyl)acetic acid on page 152 of the specification shows the final step in the synthesis and refers back to the compound prepared in Example 8(8) (specification, page 138-9) as a precursor. Example 8(8) in turn refers back to Reference example 4, Reference example 5, and Example 7 (specification, page 136-8) for the precursors needed to synthesize the final product.

4a. In Reference example 4, the compound N-methoxy-N-methyl-(3,4,5-trimethoxyphenyl)carboxamide is synthesized as a representative example. The experimental procedure used in making the compound in Reference example 4 is the same procedure to be used in synthesizing the A ring substituent in the aforementioned

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example, (4-{2-[(3,5-dimethoxy-4-methylphenyl)-(hydroxy)methyl]-5-phenylpentyl}phenyl)acetic acid. This A ring in this compound contains a 2,5-dimethoxyphenyl ring, not a 3,4,5-trimethoxyphenyl ring as in Reference example 4 in its final product.

The first step of this 2-step reaction involves the use of a harsh acylating reagent, oxalyl chloride to form an acyl chloride. While the applicant's Reference example has no substituents or R¹ groups that will react with oxalyl chloride, Claim 68 allows for numerous other R¹ groups to exist. According to known organic chemistry literature, should R¹ be any one of numerous other groups claimed, a conversion of these groups would occur resulting in a different compound, which likely would fall outside of the scope of the claims.

A few examples are shown here: if ring A represents an indole ring, an addition of the oxalyl chloride could occur to the indole ring (Aldrich Technical Bulletin AL-110, *p. 2; ref. 13*). If ring A represents a thiazole ring, a side reaction could occur adding a carboxylic acid to the thiazole (Aldrich Technical Bulletin AL-110, *p. 2; ref. 16*). If the A ring with its R¹ group was an unsaturated ring with a carbonyl substituent, it could give rise to a chlorination side product (Encyclopedia of Reagents for Organic Synthesis, "oxalyl chloride"; *p.6, para.1*). If the R¹ group was an alcohol, an addition of the oxalyl chloride could form (Aldrich Technical Bulletin AL-110, *p. 2; ref. 20*). If the R¹ group is a primary amide, an isocyanate could form (Aldrich Technical Bulletin AL-110, *p. 2; ref. 21*). If the R¹ group was a phenol, an addition of the oxalyl chloride could form (Aldrich Technical Bulletin AL-110, *p. 2; ref. 22*). If the R¹ group is a substituted amide, an imine formation would occur (Aldrich Technical Bulletin AL-110, *p. 2; ref. 23,24*). If

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the R¹ group is an amino group, it would be converted into an isocyanate (US 4,663,473; *col.3 para. 4*), alkenyl, alkynyl (J.Amer.Chem.Soc. **64**, 333, *col.1, para.2*) would also undergo some side reaction and not be considered a viable way of synthesizing said compounds.

4b. The reaction involved in Reference example 7 also uses a harsh reagent for deprotonating, lithium diisopropylamine, to form an acyl chloride. This is done so that the two pieces of the final compound can be brought together. The first piece contains Ring A and Ring B while the second piece contains Ring D and Ring E. While the applicant's Reference example again has no R¹, R², R³, or R⁴, or R⁵ groups that will react or interact with lithium diisopropylamine, Claim 68 allows for numerous other R¹, R², R³, or R⁴, or R⁵ groups to exist. According to known organic chemistry literature, should R¹, R², R³, or R⁴, or R⁵ be any one of numerous other groups claimed, a conversion of these groups would likely occur. Certain groups will be reactive with lithium diisopropylamine, and will create a second location for the lithiation reaction to take place, most likely resulting in a different compound, which would fall outside of the scope of the claims.

A few examples are shown here: if the R¹, R², R³, or R⁴, or R⁵ groups on any one of the rings were to represent a ketone, as per (17) in Claim 68, an addition of the phenoxybenzoic acid could occur on the α carbon of this ketone instead of at the α carbon to the butanone desired (Encyclopedia of Reagents for Organic Synthesis, "*lithium diisopropylamide*"; *p.2, para.1-2*). If the R¹, R², R³, or R⁴, or R⁵ groups on any one of the rings were to represent an amide, as per (12) in Claim 68, an aromatic metalation may occur causing a group to add to the alkyl group, instead of at the α carbon to the butanone

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desired (Encyclopedia of Reagents for Organic Synthesis, "*lithium diisopropylamide*"; p.15, para.1). If the R^1 , R^2 , R^3 , or R^4 , or R^5 groups were to represent a bromide group on a phenyl ring, as per (4) in Claim 68, a lithiation onto the phenyl ring could occur instead of at the α carbon to the butanone desired (Encyclopedia of Reagents for Organic Synthesis, "*lithium diisopropylamide*"; p.15, para.2). If the R^1 , R^2 , R^3 , or R^4 groups were to represent an alkyl group in the ortho position to a carboxylic acid group on a phenyl ring, as per ((1) and (18) in Claim 68, an addition could occur on the alkyl group of the phenyl ring instead of at the α carbon to the butanone desired (Encyclopedia of Reagents for Organic Synthesis, "*lithium diisopropylamide*"; p.16, para.1-2).

4c. The reaction involved in the final step of synthesizing (4-{2-[(3,5-dimethoxy-4-methylphenyl)-(hydroxy)methyl]-5-phenylpentyl}phenyl)acetic acid uses a reducing agent, sodium borohydride, for reducing the carbonyl of the precursor compound down to form the secondary alcohol. This is the final step in forming a compound of the formula I-B. While the applicant's Reference example again has no R^1 , R^2 , R^3 , or R^4 , or R^5 groups that will react with sodium borohydride, Claim 68 allows for numerous other R^1 , R^2 , R^3 , or R^4 , or R^5 groups to exist. According to known organic chemistry literature, should R^1 , R^2 , R^3 , or R^4 , or R^5 be any one of numerous other groups claimed, a conversion of these groups could occur. Should these groups be reactive with sodium borohydride, it may create unexpected side reactions, resulting in a different compound, which likely would fall outside of the scope of the claims.

A few examples are shown here: if the R^1 , R^2 , R^3 , R^4 , or R^5 groups on any one of the rings were to represent a ketone, as per (17) in Claim 68, the ketone would reduce down to a secondary alcohol, in the same fashion as the ketone that is to reduce in the

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final step to form (4-{2-[(3,5-dimethoxy-4-methylphenyl)-(hydroxy)methyl]-5-phenylpentyl}phenyl)acetic acid (Encyclopedia of Reagents for Organic Synthesis, "*sodium borohydride*"; p.1, para.8). If the R¹, R², R³, R⁴ or R⁵ groups on any one of the rings were to represent a carboxylic acid ester, as per (18) in Claim 68, the carboxylic ester would reduce down to a primary alcohol, in similar fashion as the ketone that is to reduce in the final step to form (4-{2-[(3,5-dimethoxy-4-methylphenyl)-(hydroxy)methyl]-5-phenylpentyl}phenyl)acetic acid (Encyclopedia of Reagents for Organic Synthesis, "*sodium borohydride*"; p.2, para.2). If the R¹, R², R³, or R⁴ groups on any one of the rings were to represent a cyano group, as per (7) in Claim 68, which is α to a nitrogen atom (for example, if one of the rings contained nitrogen atoms) the cyano group can be replaced by hydrogen upon reaction with the sodium borohydride. (Encyclopedia of Reagents for Organic Synthesis, "*sodium borohydride*"; p.7, para.5).

5. Furthermore, no biological testing data is provided for any of the instantly claimed compounds. Examples should be of sufficient scope as to justify the scope of the claim. Here only one compound has been synthesized to represent a large class of molecules. The definitions of the various A, B, D, and E rings as well as the R¹, R², R³, or R⁴ groups embrace many structurally divergent groups not represented at all in testing since testing for the instant compounds is not seen in the specification. Markush claims must be provided with support in the disclosure when the "working examples" fail to include written description(s) which teach how to make and use Markush members embraced thereby in full, clear and exact terms. See *In re Fouch*, 169 USPQ 429.

This area of activity can be expected to be highly structure specific and unpredictable, as is generally true for chemically-based pharmacological activity. In view

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of the structural divergence in the claims, one skilled in the art could not reasonably extrapolate the activities of some of the claimed compounds to the other structurally divergent compounds embraced by the claims which have not been tested. In cases directed to chemical compounds which are being used for their physiological activity, the scope of the claims must have a reasonable correlation to the scope of enablement provided by the specification. See *In re Surrey* 151 USPQ 724 regarding sufficiency of disclosure for a Markush group. No reasonable assurance has been made that the instant compounds as an entire class have the required activities needed to practice the invention.

Thus, factors such as "predictability", sufficient working examples," and the level of "skill in the art" have been demonstrated to be sufficiently lacking in the instant case for the scope being claimed.

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claim 1 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites the limitation "A represents an acidic group" in line 20. In formula I, there is no A group present. There is insufficient antecedent basis for this limitation in the claim. Examiner feels applicant may have meant "Z" in place of "A" to be recited in Claim 1, line 20. Appropriate correction is required.

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Conclusion

8. Claims 1-2, and 68 are rejected.
9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey H. Murray whose telephone number is 571-272-9023. The examiner can normally be reached on M-F 7:30-5pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisors, Cecilia Tsang can be reached at 571-272-0562 or Janet Andres can be reached at 571-272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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